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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,512	04/30/2001	K. Roger Aoki	D2935CON	3427

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/29/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/845,512	AOKI ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,18,19,21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,16,18,19,21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ___.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/12/06 has been entered.

2. The rejection of claims 14, 16, 18, 19, 21, 23 & 25-26 under 35 U.S.C. 112, first paragraph, for new matter is withdrawn due to the amendment of the claims.

3. The rejection of claims 25-26 on the grounds of *res judicata* (MPEP 706.03 (w)), as the issues presented by these claims are the same as those decided by the Board of Appeals and Interferences in a decision dated November 28, 2000 (*Ex parte* Aoki et al., Appeal No. 1997-2367) is withdrawn due to the cancellation of these claims.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Applicants' arguments filed 10/12/06 have been fully considered but they are not deemed to be persuasive.

6. Claims 14, 16, 18, 19, 21, 23 & 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons previously made of record for old claims 11 & 13 in Paper NO: 20040624, 20050830 & 20060502, as follows.

In contrast to Applicants' assertions on pages 5-6 of the response, and as previously made of record, the recitation of a "to ***substantially*** alleviate a [undefined] symptom..." is still indefinite because it remains unclear when "***substantially*** alleviat[ion]" is no longer "*substantially*" alleviating a symptom. In other words, the term "substantially alleviate" in claims 14 & 19 is a relative term which renders the claim indefinite. The term "substantially alleviate" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In addition, the recitation of an "alleviating activity *of from one to four days"* is ambiguous and meaningless because "of from one to four days" is not an activity, and therefore, defines nothing.

It is suggested that amending the claims appropriately to recite "as determined by... [to substantially alleviate a symptom of the spasmodic toticollis] to relax the muscle afflicted by the spasm", and deleting the redundant recitations of "[that has a spasmodic torticollis alleviating activity of from one to four days]", and "[to thereby again achieve a substantial alleviation of a symptom of the spasmodic torticollis]", as described, for example, on page 1 of the specification, should obviate both these rejections.

7. Claims 14, 16, 18, 19, 21 & 23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ludlow et al. (IDS Ref #ac), in view of Simpson et al. (IDS Ref #ag) and Janovic et al. (IDS Ref #ae), for the reasons made of record for in Paper NOs: 20040624, 20041213, 20050830 & 20060502, and as follows.

In contrast to Applicants' arguments on pages 7-8 of the response, as previously made of record, the issue remains that the claims recite "administering up to 1000 units of a botulinum toxin type A", and then "administering up to 300 units of a botulinum type E", or "wherein the amount of botulinum type A is less then 500 units". Thus, Applicants' assertion that "[t]here is no mention or suggestion in Ludlow et al. to use other botulinum toxin types..." is simply incorrect. Moreover, and in contrast, the indefinite recitation of an "alleviating activity *of from one to four days"* is meaningless" because this is a property of the amount of BoNT given, which is already defined within the claims.

Accordingly, as previously made of record, the ranges broadly recited in the claims are reasonably met by the teachings of Ludlow et al., **in view of** Simpson et al. **and** Janovic et al., which is further consistent with that upheld by the court in *Ex parte* Aoki et al., Appeal No. 1997-2367, for the reasons extensively made of record. *In arguendo*, a difference of "nine" fold in efficacy is encompassed within the ranges claimed and the dosages suggested by the teachings of Ludlow et al., **in view of** Simpson et al. **and** Janovic et al., and therefore, remains consistent with that upheld by the court in *Ex parte* Aoki et al., Appeal No. 1997-2367. Accordingly, the Board in *Ex parte* Aoki et al., Appeal No. 1997-2367) itself stated that:

> "We would remind appellants that absolute predictability is not required. For obviousness under 103, all that is required is a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)."

Second, and in contrast to Applicants' assertions that this rejection is "[i]mpermissible hindsight reconstruction", Ludlow clearly teach treating spasmodic "torticollis" using different BoTNs after a reduced response to type A toxin. The teachings of Simpson and Jankovic et al then supplement the teachings of Ludlow on why one of ordinary skill in the art would then use other specific BoTN toxins besides type F (i.e., type E) when administration with type A toxin affects are eventually reduced, and therefore, no longer feasible, for the reasons previously made of record.

In summary, Ludlow et al teach the treatment of neuromuscular disorders such as **torticollis** (i.e., **cervical dystonia**) and oromandibular **dystonia** (movement disorders characterized by muscle spasm/spasmodic activity) by intramuscular injection of botulinum toxin type F after the patients had already been treated with botulinum toxin type A (i.e., with 1/4 of the dose of type A; pg. 350, 1st full *pp*) and had developed neutralizing antibodies to the type A toxin (i.e., as manifested as a reduced response to type A toxin; pages 349-350; as it relates to claims 19 & 25-26). In particular, Ludlow teach individual dosages of "up to 300 units" in Table 1 for the second botulinum (type F) injections (e.g., patient 1: 285 twice + 150 = 720; as it relates to claims 14 & 19). Ludlow also teach treatment of patients with "up to 300 units" of the second botulinum toxin (e.g. 40 units; Table 1; as it relates to claims 14 & 19), which means that 160 units of botulinum toxin type A was previously administered (i.e., as it relates to being "up to 1000/500 units" of type A, as it relates to claims 14, 16, 19 & 21); and "from 80 units to 460

units" of type A, as it relates to claims 16, 18, 21 & 23). However, Ludlow et al do not teach administration of botulinum toxin type E after administration of botulinum toxin type A.

Simpson et al teach that all of the botulinum serotypes A, B, C1, C2, D, E, F and G are produced by the same species of bacterium, and provide a review of their pharmaceutical activities. In particular, all of the botulinum serotypes block acetylcholine release for nerve endings, and each of the serotypes are taught to be "**antigenically distinct**" (e.g., pages 155-156). Therefore, it is reasonable to expect that administration of any of the serotypes would produce the same physiological effect of blocking cholinergic neuronal transmission by "interrupt[ing] transmission at the muscle end organ" (i.e., reduced muscle spasm/twitch/ dystonias; pages 163-164 & 167). Accordingly, because the serotypes differ antigenically, antibodies developed against a first administered serotype would not be expected to block the activity of a second serotype at the cholinergic receptor. This is consistent with the teachings of Ludlow et al, who teach that the advantage of administering a second serotype toxin is to overcome the reduced responsiveness to the first toxin.

Further, consistent with both the teachings of Ludlow et al and Simpson et al, Jankovic et al teach that botulinum toxin is used for the treatment of neuromuscular disorders such as muscle spasm/back spasms, strabismus, comitant and vertical strabismus, lateral rectus palsy, nystagmus, dysthyroid myopathy, writer's cramp, blepharospasm (page 1187, first column); Wilson's disease, tardive **dystonia**, laryngeal **dystonia**, tardive dyskinesia, Parkinson's and limb/foot focal **dystonia**, tremor (pages 1187, second column & 1190, second column; Table 1); tics, segmental myoclonus, spasms due to chronic multiple sclerosis, spasms due to abnormal bladder control in patients with spinal cord injury, anismus (page 1191, second column).

Jankovic et al also teach that "blocking"/neutralizing antibodies develop to the toxin, which thereby reasonably cause patients to show to "substantially alleviate a symptom of the dystonia" to the toxin (page 1189, column 1; as it relates to claims 14, 19 & 25). Jankovic et al then conclude that "[i]t is likely that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from type A" (page 1189, column 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use Ludlow's methods of administering botulinum toxin type A to treat movement disorders characterized by muscle spasm/dystonia, followed by administration of another botulinum toxin, such as type E as taught by Simpson or Jankovic, in order to continue reducing muscle spasms/dystonia in these patients. It is emphasized that both Simpson et al and Jankovic specifically suggest administration another botulinum serotype toxin after patients become nonresponsive to a first botulinum toxin (i.e., type A). In that Ludlow teach that a reduced response to type A toxin probably is due to development of neutralizing antibodies to the type A toxin, administration after a "loss of clinical responsiveness" in clinical symptoms would be obvious, in order to maintain a positive clinical response for the patient.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
December 19, 2006

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER